REMARKS

The Office Action of September 6, 2007 includes a 35 U.S.C. § 112 rejection of Claims 1-4. It also includes a 35 U.S.C. § 103(a) rejection of Claims 1 and 2. However, Claims 3 and 4 contain allowable subject matter.

Claims 1-4 have now been amended to obviate the indefiniteness rejection. That leaves Claims 1 and 2 at issue. Applicants respectfully request reconsideration of the § 103(a) rejection of Claims 1 and 2.

Claims 1-2 were rejected under 35 U.S.C. § 103(a) over Horikawa et al. Alternatively, they were rejected over the Sakurai publication, or Horikawa et al., in view of EP 188816 or Sunagawa et al. Regarding the prior art rejections, the Examiner discussed the references in the following order.

According to the Examiner, Sakurai (see the conversion of 18 to 19 in scheme 4) this corresponds to the Claim 2 reaction in which R2 is t-butyl and dissopropylethylamine was used as base. The sole difference, according to the Examiner, is that Claim 2 calls for the trimethylsilyl protecting group while the prior art has the t-butyldimethylsily protecting group. The Examiner contends that this is a very small difference in that both are trialkylsiyl protecting group and are protected an OH group at a remote point, i.e., not at the reacting site.

According to the Examiner, Horikawa et al. (see step 4 of example 6) basically has the same teaching, albeit with a different thiol being reacted. Horikawa et al. teaches that the protecting group can be triloweralkysilyl (see column 2, lines 59-60). Since trimethylsilyl is the simplest triloweralkylsiyl, it would be understood by one of ordinary skill in the art to be an alternative to the t-butyldimethlsilyl used in the example. In addition, for the R4=H option in the rejected claims, the definition of R1 in the reference includes the unprotected OH. In other words, the reference effectively says that the OH "may be protected". Accordingly; the Examiner contends that Horikawa et al. alone renders the use of the unprotected OH or the OH protected by trimethylsilyl to be obvious.

The Examiner also contends that the Sakurai reference establishes that the art considers the two to be alternatively useable in the reaction. Page 23 (IX) to (VII) of Sakurai shows the reaction here. X' is taught as a protected OH group (page 14, line 1-2).

L is taught as the active ester of an OH group (page 21, lines 12-13). The active ester of diphenylphosphoric acid, i.e., the exact one used here, is taught at the 10th and 9th from last lines of page 21. Page 3, lines 9-10, teaches exactly two choices for silyl protecting groups, viz, the trimethylsilyl protecting group of the claims and the t-butyldimethylsilyl of the primary references, establishing the two as equivalent. Indeed, example 13 shows the use of the trimethylsilyl protecting group. The exact details are not given at that point, but the example refers to example 11-3, which in fact has the t-butyldimethysilyl group, again emphasizing the fact that these are alternatively used. Example 11-3 is the same as the applicants' (overall) process. The cyclization, and phosphorylation, correspond to what appears in applicants' specification, page 21, second step. Indeed, the reagent used in example 11-3, diphenylchlorophosphate, and used by applicants in reference example 3, is the same, albeit the compound is named differently. This is then reacted with the thiol, as seen on page E-58 of the Sakurai reference. In addition, this reference clearly teaches that the displacement with the tiol can be done with the OH unprotected (note that R4 in claim 1 can be H). See page E-51 of Sakurai in that regard.

According to the Examiner, a similar teaching appears in Sunagawa et al., this time for the triethylsilyl group. The overall reaction is seen in column 48, IV to III to V. There X is a protected OH Group, and three trialkyl silyl groups are named at column 3, lines 5-7; trimethylsilyl group, triethylsilyl group, and t-butyldimethylsilyl group. The Examiner contends this again establishes that these are considered alternatively useable. L is again taught as the active ester of an OH group and, specifically, the active ester of diphenylphosphoric acid (column 5 line 7). The use of the triethylsilyl group is seen in example 7.

Thus, in the aforedescribed circumstances, the Examiner argues that the applicants' for Claims 1 and 2 have simply substituted one known element (a protecting group) for another to perform the same function. The Examiner argues that this element, and its function, having been shown to be known in the art, would conclude that one of ordinary skill in the art could have substituted one known element for another. The Examiner concludes that the results would have been predictable because that is precisely the teaching of the secondary reference, whereby there would be a reasonable expectation of success, since success was indeed achieved with the alternative element

(the trimethylsilyl protecting group) in the secondary references. The result, according to the Examiner, is that the claimed process would have been obvious.

The applicants respond to the foregoing rejection analyses by acknowledging that the Horikawa et al. reference (example 6) discloses a method of producing a compound which corresponds to a compound (2) of the present invention. Horikawa et al. discloses a compound having tert-butyldimethylsilyl (TBS) group as R_4. Likewise, the Sakurai publication only discloses a compound having TBS group as R_4. The Examiner insists in the Office Action that the difference looks very small. However, that difference produces a big difference in effect. Applicants' submit that the big difference in effect is unexpected, and evidences patentable invention.

Specifically, Horikawa et al (example 7), disclose the method of producing a carbapenem compound through a compound (1) having TBS group, and the TBS group is deprotected by tetrabutylammoniumfluoride. However, a special reagent is required to deprotect the TBS group and it causes problems in cost, facilities, yield, and so on. Specifically, a large amount of an expensive reagent, such as tetrabutylammoniumfluoride or tetrabutylammoniumchloride/potassiumfluoride-dihydrate is used to deprotect the TBS group (as described in JP 08-027152). Moreover, production facilities with a glass lining which are usually used for producing an organic compound, cannot be used for the method using a fluorine compound. Furthermore, a strong inorganic or organic acid for deprotection of the TBS group causes yield loss of an unstable compound in an acid.

On the other hand, in the present invention the trimethylsily (TMS) group, or triethylsilyl (TES) group, is deprotected by controlling pH of a reaction mixture in mild acidic condition, as described on page 16, line 22 to page 17 of the present specification. According to the present invention, a carbapenem compound is effectively produced without yield loss. There is neither description nor suggestion of that in Horikawa et al. and Sakurai. As such, applicants submit that the present invention could not have been obvious in view of Horikawa et al. and Sakurai.

As is known, the injection of carbapenem type antibiotics has been well-researched. Recently, oral carbapenem type antibiotics have also been well-researched. The present invention is a production process which is not shown in any prior art reference

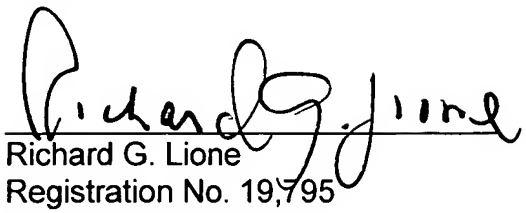
and which is simple and very cost effective compared to the prior art. Applicants submit that it is solves a long felt need and is unobvious as a result.

Finally, the Examiner says that EP 188816 reference discloses two choices for silyl protecting groups including TMS and an example relating to a compound having TMS protecting group. Applicants submit that TMS is one of a lot of protecting groups, and it is difficult to choose TMS from the protecting groups. Moreover, in a carbapenem compound of example 13 the protecting group of the carboxylate residue at the 3-position carbon is p-nitrobenzyl (PNB) group, and it is stable in a strong acid unlike alkanoyloxymethyl group of the carboxylate residue in the present invention. Accordingly, one skilled in the art would never combine the teaching of the EP 188816 reference with Sakurai or Horikawa et al. The same can be said for Sunagawa et al.

In addition, as to a compound (2) having H as R4, the compound of the present invention is different from the compound shown on page E-51 of the EP 188816 reference. Example 17 of the EP 188816 reference shows the compound which has the same chemical formula as the compound of the present invention (but has a different configuration). But it is impossible to obtain a compound (2) having H as R4 from the compound of example 17, because TBS groups is deprotected by using a fluorine compound, reacting in a strong acid aqueous solution, or reacting in a weak acid aqueous solution for long hours and such ways promote decomposition of an alkanoyloxymethyl moiety of carboxylate residue, phosphoric ester moiety and five membered ring structure (as described on page 7 of the present application (description about "Protective Groups in Organic Synthesis")). In fact, there is no example of a compound (2) having H as R4 in the references shown in the Office Action.

The sum and substance of the foregoing is that the applicants have invented a process which differs from that of any prior art process. The difference appears to be small but, like many for producing valuable compounds, it is critically different. Applicants submit that the critical difference is, no way, something which the prior suggests or intimates as desirable. As such, the claim process should be patentable.

Respectfully submitted,



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